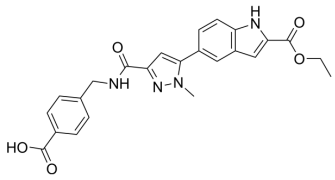
BI-4394

Cat. No.:	HY-124029
CAS No.:	1222173-37-6
Molecular Formula:	$C_{24}H_{22}N_4O_5$
Molecular Weight:	446.46
Target:	MMP
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (223.98 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2398 mL	11.1992 mL	22.3984 mL
	5 mM	0.4480 mL	2.2398 mL	4.4797 mL
	10 mM	0.2240 mL	1.1199 mL	2.2398 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

BI-4394 (MMP13-IN-3) is a potent, selective, and orally active MMP-13 inhibitor (IC_{50}=1 nM[1]) for the potential treatment of osteoarthritis[2]. BI-4394 is >1000 selective over other MMPs[1].

IC_{50} & Target

MMP-13 1 nM (IC_{50})	MMP-14 8.3 μM (IC_{50})	MMP-9 8.9 μM (IC_{50})	MMP-10 16 μM (IC_{50})
MMP-2 18 μM (IC_{50})			

In Vitro

BI-4394 (Compound 15) is potent in a full-length MMP-13 collagen degradation assay (11 nM) and is able to inhibit degradation of bovine nasal cartilage with an IC_{50} of 31 nM. BI-4394 inhibits MMP-2, MMP-9, MMP-10 and MMP-14 with IC_{50}s of 18, 8.9, 16 and 8.3 μM, respectively[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

When dosed orally at 10 mg/kg or i.v. 1 mg/kg, BI-4394 (Compound 15) reaches micromolar plasma levels (AUC=1109±64 nM

h/mL), displays modest clearance (CL=34 mL/min/kg), and shows acceptable bioavailability (39%). The V_{ss} is quite low at 0.26 mL/mi/kg rat pharmacokinetic profile. BI-4394 has short terminal elimination half-life ($t_{1/2}$=0.47 h for rat (1 mg/kg, i.v.) and rat (10 mg/kg, orally), respectively)[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Srapgue Dally Rats[1]
Dosage:	10 mg/kg (oral gavage); 1 mg/kg (i.v.)
Administration:	Dosed orally (10 mg/kg); i.v. (1 mg/kg)(Pharmacokinetic Analysis)
Result:	$T_{1/2}$=0.47 h for rat (1 mg/kg, i.v.) and rat (10 mg/kg, orally) , respectively.

REFERENCES

[1]. Taylor SJ, et al. Fragment-based discovery of indole inhibitors of matrix metalloproteinase-13. J Med Chem. 2011 Dec 8;54(23):8174-87.

[2]. Ruminski PG, et al. Discovery of N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide. A Highly Selective and Orally Bioavailable Matrix Metalloproteinase-13 Inhibitor for the Potential Treatment of Osteoarthritis. J Med Chem. 2016 Jan 14;59(1):313-27.

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